60. (Amended) The method according to claim **[40]** **63**, wherein the associating compound is designed to introduce a non-polar group which occupies the S1' pocket of TNF-α-converting enzyme.

61. (Amended) The method according to claim **[40]** **63**, wherein the associating compound is designed to introduce a group which lies within the channel joining S1' - S3' pockets of TNF-α-converting enzyme and which makes appropriate van der Waal contact with the channel.

62. (Amended) The method according to claim **[40]** **63**, wherein the associating compound is designed to form a hydrogen bond with Leu348 or Gly349 on the backbone amide groups of TNF-α-converting enzyme.

REMARKS

Claim 40 has been cancelled, and claims 63-65 have been added. Claims 41-65 are pending.

I. OBJECTIONS

The examiner objects to the description provided for Figure 2, allegedly that it mentions colors not present in the figure itself. Applicants will soon provide formal, color drawings and, thereby, obviate the examiner's objection.

The examiner also objects to claim 43 for referencing Table 1. Applicants assert that the claim's reference to Table 1 is allowable under MPEP § 2173.05(s). Table 1 provides thirty-seven (37) pages of atomic coordinate data. Because applicants presently have no practical way of defining the invention in words alone, and because it would be more concise to incorporate the table by reference than reproduce it in the claim, Applicants assert that the instant circumstance satisfies the prerequisites detailed in MPEP § 2173.05(s) for incorporation by reference. Applicants therefore request that this objection be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112, ¶1

The examiner rejects claims 40-62 under 35 U.S.C. §112, ¶1, alleging that the claims are not enabled by the specification. In particular, of the rejection, the examiner argues that the "[b]inding of one hydroxamate-based compound . . . does not fairly suggest that TACE will similarly bind to other compounds encompassed by the broad genus of hydroxamate-based compounds, or even other compounds outside of the genus . . . ." Office Action, page 3, second paragraph. The examiner also contends that "the specification fails to sufficiently teach of the

association of binding compounds that are not inhibitors" and, further, that "simplified models do not predict the binding of a ligand." *Id.* Finally, the examiner asserts that claims are not enabled allegedly because "[t]he disclosed co-crystal structure is not necessarily representative of the native protein structure to which the designed associating compounds will be targeting." Office Action, page 4, second paragraph.

Applicants respectfully disagree with these assertions. As illuminated by *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), and related precedent, the touchstone for enablement is not whether any experimentation is necessary, but whether any experimentation that is needed would be deemed undue, given the type and amount of experimentation that is typical in the area. *See* MPEP §2164.01 (7th ed., July 1998) at page 2100-146, column 1. In this instance, the examiner has not met the PTO's burden of demonstrating that one skilled in the art, at the time of the invention, would have had to engage in undue experimentation to make or use the claimed invention.

For a perspective on what would be "routine" (not undue) experimentation in this context, applicants note that the present invention invokes atomic coordinates obtained from crystallographical analysis of a TACE polypeptide, to the ends of designing an associating compound for the polypeptide that forms a bond with the TACE catalytic domain. The use of atomic coordinates for molecular design is well-known to the art, and has proven an effective approach for selecting and synthesizing compounds that associate with peptides of interest. Despite this effectiveness, however, practitioners do not anticipate every designed molecule to be a lead candidate for further development. Rather, the expectation is that the crystallized structure will aide in the design effort, by delineating the required size and shape of putative ligands.

Contrary to the examiner's assertion, binding models based on crystalline structures ***do*** predict the binding of putative ligands. This understanding is not undercut by Rutenber *et al.* (1993), as cited by the examiner, because Rutenber demonstrated that putative ligands can be identified *via* computational screening. Based on binding models, Rutenber modified the compound haloperidol to enhance its inhibitory effect on HIV-1 protease. As noted by the examiner, the observed ligand-enzyme binding differed somewhat from that predicted by the computational search. The models were predictive, however, for binding between the ligand and a protease variant, HIV-1 protease Q7K. *See Id.* at page 15344, column 2 and Figure 3. Moreover, the lead compound itself, *i.e.* haloperidol, was identified using a computational screen of the Cambridge Structural Database. *See* Desjarlais *et al.*, *PNAS* 87:664-6648 (1993). Thus, the limitations discussed by Rutenber did not alter the effectiveness of the method in identifying putative ligands. In fact, the authors remark that "[d]espite these limitations, this structure based approach aided in developing a unique inhibitor with a K_i = 15μM and offers an important alternative to the often rate-limiting step in drug development." Rutenber at 15346, last paragraph.

In any event, the state of the relevant technology has advanced dramatically in the decade since Rutenber, and the predictability of binding modes had improved significantly by the time of the present invention. As the appended abstracts evidence, modern docking algorithms, circa 1998, were very successful at predicting binding ligands (see enclosed list, entitled "Docking Algorithms"). Also, modern binding models can incorporate molecular water and counterions (or, in the case of TACE, metals) into the calculation, and a modest amount of protein flexibility can be included. Thus, multiple conformational states of the binding ligand can be evaluated, the examiner's contrary contention notwithstanding. See the present specification at page 78, lines 17-22.

Also indicative of the predictability of the claimed methodology is the fact that applicants have designed numerous molecules, based upon the crystal structure of TACE, and have co-crystallized 14 additional TACE-ligand complexes. As shown in enclosed Table 1, the additional ligands, examples 3-16, differ little from the co-crystal structure elucidated in the specification.

With respect to the suggestion that "the specification fails to sufficiently teach of the association of binding compounds that are not inhibitors," applicants believe that the examiner has mischaracterized their disclosure of the present invention. Binding models utilizing atomic coordinates obtained from crystallographical analysis of a TACE polypeptide identify associating compounds that bind with the catalytic domain of the TACE polypeptide. The present invention teaches that, in addition to inhibitors, such associating compounds can include "compounds that act as mediators or other regulatory compounds." Application at page 19, lines 14-16. Thus, the present invention provides methods of identifying compounds which associate with the catalytic domain of a TACE polypeptide, regardless of the compound's effect on the polypeptide.

Regarding the examiner's asserted requirement for native TACE, applicants respectfully submit that molecular modeling that employs the co-crystal of the binding domain is predictive of binding of the entire protein. In this regard, structure-based designs that use truncated proteins provide a predictable means for designing ligands. As further support for this proposition, a comparison of binding studies of two ligands to the catalytic domain (CAT) and the catalytic-disintegrin (CAT-DIS) domain of TACE is provided. The two ligands, identified as examples 1 and 2, respectively, correspond to the first two compounds identified in enclosed Table 1. As shown in the table, example 1 is a truncated version of example 2. The graphs demonstrate the negligible difference in ligand binding between the native and truncated forms of the peptide.

The examiner also rejects claims 48-49 under 35 U.S.C. §112, ¶1, contending that the specification does not teach one skilled in the art how to co-crystallize a TACE polypeptide along with its binding partner. Applicants respectfully traverse these rejections.

In implementing the present invention, Applicants have not failed to co-crystallize a TACE-ligand complex. To date, 14 additional TACE-ligand complexes have been co-crystallized. As

shown in enclosed Table 1, the additional ligands, examples 3-16, differ little from the co-crystal structure elucidated in the specification. Accordingly, Applicants assert that the examiner's objections regarding the scope of the invention's teachings are unwarranted.

In summary, one of ordinary skill in the art, informed by the instant specification, could readily use applicants' inventive methodology to design, without undue experimentation, a ligand that associates with the TACE catalytic domain. Accordingly, applicants have satisfied the enablement requirement under Section 112.

III. REJECTIONS UNDER 35 U.S.C. §112, ¶2

The examiner rejects claims 40-62 under 35 U.S.C. §112, ¶2, for allegedly being indefinite. Applicants respectfully traverse these rejections.

The examiner asserts that the abbreviation "TNF-α" is unclear and suggests that the full name be spelled out at it first appearance. The proposed amendment conforms to the examiner's preferences and obviates the rejection.

According to the examiner, moreover, the phrase "catalytic domain" is indefinite because the "specification and claims do not indicate what residues constitute the beginning and end of the recited domain." Applicants respectfully traverse this assertion. The specification teaches that TACE "has recently been identified as a zinc endopeptidase consisting of an extracellular region comprising an N-terminal signal peptide, a pro-domain, *a 263 residue catalytic domain (TCD) that is preceded by a furin cleavage site (residues 211-214), a disintegrin domain*, an EGF-like domain, and a crambin-like domain, an apparent transmembrane helix and the intracellular C-terminal tail." Application at page 2, lines 8-12 (emphasis added). In other words, the application defines the catalytic domain of TACE as starting after the furin cleavage site (residue 215) and ending prior to the disintegrin domain, *i.e.* residue 477. Accordingly, one of ordinary skill would understand readily the metes and bounds of the claim term, in light of the specification and published PCT application No. WO 96/41624, which was incorporated by reference. Applicants request, therefore, that this rejection be withdrawn.

The examiner further asserts that the term "said polypeptide" lacks sufficient antecedent support. It is believed that the proposed amendments obviate this rejection.

Also, the proposed amendments address the examiner's concern that the phrase "diffraction coordinates" is indefinite. Thus, claim 63 recites the identification of a TACE-associating compound by using atomic coordinates obtained from crystallographical analysis of a TACE polypeptide. The proposed amendments conform to the examiner's preferences and obviate this rejection

IV. REJECTIONS UNDER 35 U.S.C. §102

The examiner rejects claims 40-42 and 56 under 35 U.S.C. §102(b), for allegedly being anticipated by Gomis-Ruth *et al.* (1998). Applicants respectfully traverse these rejections.

The examiner asserts that Gomis-Ruth teaches "a method for identifying a compound that associates with TNF-α converting enzyme (TACE) using a theoretical crystal structure of the TACE polypeptide based on structural sequence alignment to the X-ray crystal structure of Adamalysin II." Office Action, paragraph bridging pages 6-7. The examiner then states that Gomis-Ruth anticipates the present invention because "the claim wording does not have a limitation preventing the theoretical modeling of a crystal structure of TACE based on a structural sequence alignment to a homologous protein." *Id.*

In reaching this conclusion, the examiner in effect has ignored elements recited in the claims. Cancelled claim 40 was directed to a "method of identifying a compound that associates with TNF-α converting enzyme, comprising designing an associating compound for said enzyme that forms a bond with the [TACE] catalytic domain *based on X-ray diffraction coordinates of a [TACE] polypeptide crystal*" (emphasis added). To reach this conclusion, the examiner has ignored the requirement that the designing step utilizes the X-ray diffraction coordinates of a TACE polypeptide crystal. In its stead, the examiner envisions a designing step utilizing *modeled* X-ray diffraction coordinates of a *theoretical* TACE polypeptide crystal.

Applicants assert that it is well-known that crystallographical analysis of a polypeptide produces X-ray diffraction coordinates, which in turn can be used to determine the atomic coordinates of a modeled protein. Nevertheless, Applicants have amended the claim to conform to the examiner's preferences.

In order to reject a claim under 35 U.S.C. §102(b), the examiner must demonstrate that each claim limitation is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986). Gomis-Ruth *et al.* cannot anticipate in this context because the reference does not teach identification of a TACE-associating compound by using atomic coordinates obtained from crystallographical analysis of a TACE polypeptide. Accordingly, applicants submit that these rejections are improper and request that they be withdrawn.

V. REJECTIONS UNDER 35 U.S.C. §103(a)

The examiner rejects claims 40-42 and 56 under 35 U.S.C. §103(a), for allegedly being unpatentable over Cirilli *et al.* in view of Gomis-Ruth *et al.* Applicants respectively traverse these rejections.

Cirilli *et al.* is cited for allegedly disclosing a theoretical crystal model of TACE based on a structural sequence alignment of the X-ray crystal structure of Adamalysin II. Cirilli does not use atomic coordinates obtained from crystallographical analysis of a TACE polypeptide. Accordingly, as noted by the examiner, "Cirilli *et al.* do not teach a method of identifying a compound that associates with the TACE catalytic domain comprised of designing an associating compound, synthesizing the compound, and determining its interaction with TACE." Office Action at page 8, third paragraph. The examiner's invocation of Gomis-Ruth *et al.*, alleged to disclose the theoretical modeling of TACE crystal based upon Adamalysin II, does not obviate the deficiencies of the primary reference. Therefore, no combination of these references would lead one of reasonable skill in the art to the claimed invention.

Accordingly, applicants assert that these rejections are improper and respectfully request that they be withdrawn.

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In view of the foregoing remarks it is believed that the application is in condition for allowance. A favorable disposition of the application therefore is solicited. The examiner also is invited to contact the undersigned if there are any questions or if the examiner believes that further discussion will advance prosecution.

Respectfully submitted,

Feb 5, 2001
Date

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